

Amendments to the Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application;

Listing of Claims:

Claims 1-187 were previously cancelled.

Claims 188—246 are currently cancelled.

New Claims 247-386 are currently added.

247. (New) A method of identifying a phenotype associated with a disruption of a gene which encodes for a PRO224, PRO9783, PRO1108, PRO34000, PRO240, PRO943, hu A33, PRO230, PRO178, PRO1199, PRO4333, PRO1336, PRO19598, PRO1083, hu TRPM2 or PRO1801 polypeptide, the method comprising:

(a) providing a non-human transgenic animal whose genome comprises a disruption of a gene which is an ortholog of a human gene that encodes for a PRO224, PRO9783, PRO1108, PRO34000, PRO240, PRO943, hu A33, PRO230, PRO178, PRO1199, PRO4333, PRO1336, PRO19598, PRO1083, hu TRPM2 or PRO1801 polypeptide;

(b) measuring a physiological characteristic of the non-human transgenic animal; and

(c) comparing the measured physiological characteristic with that of a gender matched wild-type animal, wherein the physiological characteristic of the non-human transgenic animal that differs from the physiological characteristic of the wild-type animal is identified as a phenotype resulting from the gene disruption in the non-human transgenic animal.

248. (New) The method of Claim 247, wherein the non-human transgenic animal is heterozygous for the disruption of a gene which encodes for a PRO224, PRO9783, PRO1108, PRO34000, PRO240, PRO943, hu A33, PRO230, PRO178, PRO1199, PRO4333, PRO1336, PRO19598, PRO1083, hu TRPM2 or PRO1801 polypeptide.

249. (New) The method of Claim 247, wherein the phenotype exhibited by the non-human transgenic animal as compared with gender matched wild-type littermates is at least one of the following: a neurological disorder; a cardiovascular, endothelial or angiogenic disorder; an eye abnormality; an immunological disorder; an oncological disorder; a bone metabolic abnormality or disorder; a lipid metabolic disorder; or a developmental abnormality.

250. (New) The method of Claim 249, wherein the neurological disorder is an increased anxiety-like response during open field activity testing.

251. (New) The method of Claim 249, wherein the neurological disorder is a decreased anxiety-like response during open field activity testing.

252. (New) The method of Claim 249, wherein the neurological disorder is an abnormal circadian rhythm during home-cage activity testing.

253. (New) The method of Claim 249, wherein the neurological disorder is an enhanced motor coordination during inverted screen testing.

254. (New) The method of Claim 249, wherein the neurological disorder is an impaired motor coordination during inverted screen testing.

255. (New) The method of Claim 249, wherein the neurological disorder is depression, generalized anxiety disorders, attention deficit disorder, sleep disorder, hyperactivity disorder, obsessive compulsive disorder, schizophrenia, cognitive disorders, hyperalgesia or sensory disorders.

256. (New) The method of Claim 249, wherein the eye abnormality is a retinal abnormality.

257. (New) The method of Claim 249, wherein the eye abnormality is consistent with vision problems or blindness.

258. (New) The method of Claim 256, wherein the retinal abnormality is consistent with retinitis pigmentosa.

259. (New) The method of Claim 256, wherein the retinal abnormality is characterized by retinal degeneration or retinal dysplasia.

260. (New) The method of Claim 256, wherein the retinal abnormality is consistent with retinal dysplasia, various retinopathies, including retinopathy of prematurity, retrolental fibroplasia, neovascular glaucoma, age-related macular degeneration, diabetic macular edema, corneal neovascularization, corneal graft neovascularization, corneal graft rejection, retinal/choroidal neovascularization, neovascularization of the angle (rubeosis), ocular neovascular disease, vascular restenosis, arteriovenous malformations (AVM), meningioma, hemangioma, angiofibroma, thyroid hyperplasias (including Grave's disease), corneal and other tissue transplantation, retinal artery obstruction or occlusion; retinal degeneration causing secondary atrophy of the retinal vasculature, retinitis pigmentosa, macular dystrophies, Stargardt's disease, congenital stationary night blindness, choroideremia, gyrate atrophy, Leber's congenital amaurosis, retinoschisis disorders, Wagner's syndrome, Usher syndromes, Zellweger syndrome, Saldino-Mainzer syndrome, Senior-Loken syndrome, Bardet-Biedl syndrome, Alport's syndrome, Alstrom's syndrome, Cockayne's syndrome, dysplasia spondyloepiphysearia congenita, Flynn-Aird syndrome, Friedreich ataxia, Hallgren syndrome, Marshall syndrome, Albers-Schnoberg disease, Refsum's disease, Kearns-Sayre syndrome, Waardenburg's syndrome, Alagile syndrome, myotonic dystrophy, olivopontocerebellar atrophy, Pierre-Marie syndrome, Stickler syndrome, carotinememia, cystinosis, Wolfram syndrome, Bassen-Kornzweig syndrome, abetalipoproteinemia, incontinentia pigmenti, Batten's disease, mucopolysaccharidoses, homocystinuria, or mannosidosis.

261. (New) The method of Claim 249, wherein the eye abnormality is a cataract.

262. (New) The method of Claim 261, wherein the cataract is consistent with systemic diseases such as human Down's syndrome, Hallerman-Streiff syndrome, Lowe syndrome, galactosemia, Marfan syndrome, Trismoy 13-15, Alport syndrome, myotonic dystrophy, Fabry disease, hypoparathyroidism or Conradi syndrome.

263. (New) The method of Claim 249, wherein the developmental abnormality comprises embryonic lethality or reduced viability.

264. (New) The method of Claim 249, wherein the cardiovascular, endothelial or angiogenic disorders are arterial diseases, such as diabetes mellitus; papilledema; optic atrophy; atherosclerosis; angina; myocardial infarctions such as acute myocardial infarctions, cardiac hypertrophy, and heart failure such as congestive heart failure; hypertension; inflammatory vasculitides; Reynaud's disease and Reynaud's phenomenon; aneurysms and arterial restenosis; venous and lymphatic disorders such as thrombophlebitis, lymphangitis, and lymphedema; peripheral vascular disease; cancer such as vascular tumors, *e.g.*, hemangioma (capillary and cavernous), glomus tumors, telangiectasia, bacillary angiomatosis, hemangioendothelioma, angiosarcoma, haemangiopericytoma, Kaposi's sarcoma, lymphangioma, and lymphangiosarcoma; tumor angiogenesis; trauma such as wounds, burns, and other injured tissue, implant fixation, scarring; ischemia reperfusion injury; rheumatoid arthritis; cerebrovascular disease; renal diseases such as acute renal failure, or osteoporosis.

265. (New) The method of Claim 249, wherein the immunological disorders are systemic lupus erythematosus; rheumatoid arthritis; juvenile chronic arthritis; spondyloarthropathies; systemic sclerosis (scleroderma); idiopathic inflammatory myopathies (dermatomyositis, polymyositis); Sjögren's syndrome; systemic vasculitis; sarcoidosis; autoimmune hemolytic anemia (immune pancytopenia, paroxysmal nocturnal hemoglobinuria); autoimmune thrombocytopenia (idiopathic thrombocytopenic purpura, immune-mediated

thrombocytopenia); thyroiditis (Grave's disease, Hashimoto's thyroiditis, juvenile lymphocytic thyroiditis, atrophic thyroiditis); diabetes mellitus; immune-mediated renal disease (glomerulonephritis, tubulointerstitial nephritis); demyelinating diseases of the central and peripheral nervous systems such as multiple sclerosis, idiopathic demyelinating polyneuropathy or Guillain-Barré syndrome, and chronic inflammatory demyelinating polyneuropathy; hepatobiliary diseases such as infectious hepatitis (hepatitis A, B, C, D, E and other non-hepatotropic viruses), autoimmune chronic active hepatitis, primary biliary cirrhosis, granulomatous hepatitis, and sclerosing cholangitis; inflammatory bowel disease (ulcerative colitis: Crohn's disease); gluten-sensitive enteropathy, and Whipple's disease; autoimmune or immune-mediated skin diseases including bullous skin diseases, erythema multiforme and contact dermatitis, psoriasis; allergic diseases such as asthma, allergic rhinitis, atopic dermatitis, food hypersensitivity and urticaria; immunologic diseases of the lung such as eosinophilic pneumonias, idiopathic pulmonary fibrosis and hypersensitivity pneumonitis; or transplantation associated diseases including graft rejection and graft -versus-host disease.

266. (New) The method of Claim 249, wherein the bone metabolic abnormality or disorder is arthritis, osteoporosis or osteopetrosis.

267. (New) The method of Claim 247, wherein the non-human transgenic animal exhibits at least one of the following physiological characteristics compared with gender matched wild-type littermates: a decreased anxiety-like response during open field activity testing; an increased anxiety-like response during open field activity testing; balding, exothalamus observations, and piloerection observations in functional observation battery (FOB) testing; an increased mean artery-to-vein ratio associated with retinal degeneration; developing cataracts; an increased mean serum cholesterol level; an increased mean serum triglyceride level; a decreased mean serum insulin level, a decreased mean percentage of B cells in the spleen and lymph node; a decreased mean serum IgG2a response to an ovalbumin challenge; decreased mean serum IgA levels; an increased mean serum IgG2a response to an ovalbumin challenge; increased mean serum IgM, IgG1, IgG2a and IgG2b levels; increased mean serum IgM, IgA and

IgG3 levels; increased mean serum IgM, IgG1, IgG2a and IgG2b levels; an increased mean percentage of CD4 cells and a decreased mean percentage of CD8 cells in spleen and thymus; mobilization of neutrophils in response to peritoneal inflammation; an enhanced DDS-induced colitis response; an enhanced ConA-induced hepatitis response; a decreased skin fibroblast proliferation; a decreased volumetric bone mineral density, a decreased bone mineral content index (BMC/LBM), and a decreased mean bone mineral density in total body, femur and vertebrae; a decreased mean bone mineral density, a decreased mean trabecular bone volume, decreased thickness, and decreased connectivity density; a decreased body weight and length, decreased total tissue mass and lean body mass, a decreased femoral midshaft cross-sectional area with decreased alkaline phosphatase levels; growth retardation with decreased body weight and length, total tissue mass, and lean body mass; a diaphragmatic hernia; an increased total tissue mass, increased lean body mass, increased bone mineral content, increased total body and increased femoral bone mineral density; an enhanced glucose tolerance; developmental disorders including abnormal kidney development marked by kidney agenesis; embryonic lethality; or embryonic lethality wherein heterozygous adults exhibited decreased serum IgM, IgG1, IgG2a, IgG2b and IgG3 levels.

268. (New) An isolated cell derived from a non-human transgenic animal whose genome comprises a disruption of a gene which is an ortholog of a human gene that encodes for a PRO224, PRO9783, PRO1108, PRO34000, PRO240, PRO943, hu A33, PRO230, PRO178, PRO1199, PRO4333, PRO1336, PRO19598, PRO1083, hu TRPM2 or PRO1801 polypeptide.

269. (New) The isolated cell of Claim 268 which is a murine cell.

270. (New) The isolated cell of Claim 269, wherein the murine cell is an embryonic stem cell.

271. (New) The isolated cell of Claim 268, wherein the non-human transgenic animal exhibits at least one of the following phenotypes compared with gender matched wild-type

littermates: a neurological disorder; a cardiovascular, endothelial or angiogenic disorder; an eye abnormality; an immunological disorder; an oncological disorder; a bone metabolic abnormality or disorder; a lipid metabolic disorder; or a developmental abnormality.

272. (New) A method of identifying an agent that modulates a phenotype associated with a disruption of a gene which encodes for a PRO224, PRO9783, PRO1108, PRO34000, PRO240, PRO943, hu A33, PRO230, PRO178, PRO1199, PRO4333, PRO1336, PRO19598, PRO1083, hu TRPM2 or PRO1801 polypeptide, the method comprising:

- (a) providing a non-human transgenic animal whose genome comprises a disruption of a gene which is an ortholog of a human gene that encodes for the PRO224, PRO9783, PRO1108, PRO34000, PRO240, PRO943, hu A33, PRO230, PRO178, PRO1199, PRO4333, PRO1336, PRO19598, PRO1083, hu TRPM2 or PRO1801 polypeptide;
- (b) measuring a physiological characteristic of the non-human transgenic animal of (a);
- (c) comparing the measured physiological characteristic of (b) with that of a gender matched wild-type animal, wherein the physiological characteristic of the non-human transgenic animal that differs from the physiological characteristic of the wild-type animal is identified as a phenotype resulting from the gene disruption in the non-human transgenic animal;
- (d) administering a test agent to the non-human transgenic animal of (a); and
- (e) determining whether the test agent modulates the identified phenotype associated with gene disruption in the non-human transgenic animal.

273. (New) The method of Claim 272, wherein the phenotype associated with the gene disruption comprises a neurological disorder; a cardiovascular, endothelial or angiogenic disorder; an eye abnormality; an immunological disorder; an oncological disorder; a bone metabolic abnormality or disorder; a lipid metabolic disorder; or a developmental abnormality.

274. (New) The method of Claim 273, wherein the neurological disorder is an increased anxiety-like response during open field activity testing.

275. (New) The method of Claim 273, wherein the neurological disorder is a decreased anxiety-like response during open field activity testing.

276. (New) The method of Claim 273, wherein the neurological disorder is an abnormal circadian rhythm during home-cage activity testing.

277. (New) The method of Claim 273, wherein the neurological disorder is an enhanced motor coordination during inverted screen testing.

278. (New) The method of Claim 273, wherein the neurological disorder is an impaired motor coordination during inverted screen testing.

279. (New) The method of Claim 273, wherein the neurological disorder is depression, generalized anxiety disorders, attention deficit disorder, sleep disorder, hyperactivity disorder, obsessive compulsive disorder, schizophrenia, cognitive disorders, hyperalgesia or sensory disorders.

280. (New) The method of Claim 273, wherein the eye abnormality is a retinal abnormality.

281. (New) The method of Claim 273, wherein the eye abnormality is consistent with vision problems or blindness.

282. (New) The method of Claim 280, wherein the retinal abnormality is consistent with retinitis pigmentosa.

283. (New) The method of Claim 280, wherein the retinal abnormality is characterized by retinal degeneration or retinal dysplasia.

284. (New) The method of Claim 280, wherein the retinal abnormality is consistent with retinal dysplasia, various retinopathies, including retinopathy of prematurity, retrolental fibroplasia, neovascular glaucoma, age-related macular degeneration, diabetic macular edema, corneal neovascularization, corneal graft neovascularization, corneal graft rejection, retinal/choroidal neovascularization, neovascularization of the angle (rubeosis), ocular neovascular disease, vascular restenosis, arteriovenous malformations (AVM), meningioma, hemangioma, angiofibroma, thyroid hyperplasias (including Grave's disease), corneal and other tissue transplantation, retinal artery obstruction or occlusion; retinal degeneration causing secondary atrophy of the retinal vasculature, retinitis pigmentosa, macular dystrophies, Stargardt's disease, congenital stationary night blindness, choroideremia, gyrate atrophy, Leber's congenital amaurosis, retinoschisis disorders, Wagner's syndrome, Usher syndromes, Zellweger syndrome, Saldino-Mainzer syndrome, Senior-Loken syndrome, Bardet-Biedl syndrome, Alport's syndrome, Alstrom's syndrome, Cockayne's syndrome, dysplasia spondyloepiphysearia congenita, Flynn-Aird syndrome, Friedreich ataxia, Hallgren syndrome, Marshall syndrome, Albers-Schnoberg disease, Refsum's disease, Kearns-Sayre syndrome, Waardenburg's syndrome, Alagille syndrome, myotonic dystrophy, olivopontocerebellar atrophy, Pierre-Marie syndrome, Stickler syndrome, carotinemia, cystinosis, Wolfram syndrome, Bassen-Kornzweig syndrome, abetalipoproteinemia, incontinentia pigmenti, Batten's disease, mucopolysaccharidoses, homocystinuria, or mannosidosis.

285. (New) The method of Claim 273, wherein the eye abnormality is a cataract.

286. (New) The method of Claim 285, wherein the cataract is consistent with systemic diseases such as human Down's syndrome, Hallerman-Streiff syndrome, Lowe syndrome, galactosemia, Marfan syndrome, Trisomy 13-15, Alport syndrome, myotonic dystrophy, Fabry disease, hypoparathyroidism or Conradi syndrome.

287. (New) The method of Claim 273, wherein the developmental abnormality comprises embryonic lethality or reduced viability.

288. (New) The method of Claim 273, wherein the cardiovascular, endothelial or angiogenic disorders are arterial diseases, such as diabetes mellitus; papilledema; optic atrophy; atherosclerosis; angina; myocardial infarctions such as acute myocardial infarctions, cardiac hypertrophy, and heart failure such as congestive heart failure; hypertension; inflammatory vasculitides; Reynaud's disease and Reynaud's phenomenon; aneurysms and arterial restenosis; venous and lymphatic disorders such as thrombophlebitis, lymphangitis, and lymphedema; peripheral vascular disease; cancer such as vascular tumors, *e.g.*, hemangioma (capillary and cavernous), glomus tumors, telangiectasia, bacillary angiomatosis, hemangioendothelioma, angiosarcoma, haemangiopericytoma, Kaposi's sarcoma, lymphangioma, and lymphangiosarcoma; tumor angiogenesis; trauma such as wounds, burns, and other injured tissue, implant fixation, scarring; ischemia reperfusion injury; rheumatoid arthritis; cerebrovascular disease; renal diseases such as acute renal failure, or osteoporosis.

289. (New) The method of Claim 273, wherein the immunological disorders are systemic lupus erythematosus; rheumatoid arthritis; juvenile chronic arthritis; spondyloarthropathies; systemic sclerosis (scleroderma); idiopathic inflammatory myopathies (dermatomyositis, polymyositis); Sjögren's syndrome; systemic vasculitis; sarcoidosis; autoimmune hemolytic anemia (immune pancytopenia, paroxysmal nocturnal hemoglobinuria); autoimmune thrombocytopenia (idiopathic thrombocytopenic purpura, immune-mediated thrombocytopenia); thyroiditis (Grave's disease, Hashimoto's thyroiditis, juvenile lymphocytic thyroiditis, atrophic thyroiditis); diabetes mellitus; immune-mediated renal disease (glomerulonephritis, tubulointerstitial nephritis); demyelinating diseases of the central and peripheral nervous systems such as multiple sclerosis, idiopathic demyelinating polyneuropathy or Guillain-Barré syndrome, and chronic inflammatory demyelinating polyneuropathy; hepatobiliary diseases such as infectious hepatitis (hepatitis A, B, C, D, E and other non-hepatotropic viruses), autoimmune chronic active hepatitis, primary biliary cirrhosis, granulomatous hepatitis, and sclerosing cholangitis; inflammatory bowel disease (ulcerative colitis: Crohn's disease); gluten-sensitive enteropathy, and Whipple's disease; autoimmune or immune-mediated skin diseases including bullous skin diseases, erythema multiforme and

contact dermatitis, psoriasis; allergic diseases such as asthma, allergic rhinitis, atopic dermatitis, food hypersensitivity and urticaria; immunologic diseases of the lung such as eosinophilic pneumonia, idiopathic pulmonary fibrosis and hypersensitivity pneumonitis; or transplantation-associated diseases including graft rejection and graft -versus-host disease.

290. (New) The method of Claim 273, wherein said bone metabolic abnormality or disorder is arthritis, osteoporosis or osteopetrosis.

291. (New) The method of Claim 272, wherein the non-human transgenic animal exhibits at least one of the following physiological characteristics compared with gender matched wild-type littermates: a decreased anxiety-like response during open field activity testing; an increased anxiety-like response during open field activity testing; balding, exothalamus observations, and piloerection observations in functional observation battery (FOB) testing; an increased mean artery-to-vein ratio associated with retinal degeneration; developing cataracts; an increased mean serum cholesterol level; an increased mean serum triglyceride level; a decreased mean serum insulin level, a decreased mean percentage of B cells in the spleen and lymph node; a decreased mean serum IgG2a response to an ovalbumin challenge; decreased mean serum IgA levels; an increased mean serum IgG2a response to an ovalbumin challenge; increased mean serum IgM, IgG1, IgG2a and IgG2b levels; increased mean serum IgM, IgA and IgG3 levels; increased mean serum IgM, IgG1, IgG2a and IgG2b levels; an increased mean percentage of CD4 cells and a decreased mean percentage of CD8 cells in spleen and thymus; mobilization of neutrophils in response to peritoneal inflammation; an enhanced DDS-induced colitis response; an enhanced ConA-induced hepatitis response; a decreased skin fibroblast proliferation; a decreased volumetric bone mineral density, a decreased bone mineral content index (BMC/LBM), and a decreased mean bone mineral density in total body, femur and vertebrae; a decreased mean bone mineral density, a decreased mean trabecular bone volume, decreased thickness, and decreased connectivity density; a decreased body weight and length, decreased total tissue mass and lean body mass, a decreased femoral midshaft cross-sectional area with decreased alkaline phosphatase levels; growth retardation with decreased body weight

and length, total tissue mass, and lean body mass; a diaphragmatic hernia; an increased total tissue mass, increased lean body mass, increased bone mineral content, increased total body and increased femoral bone mineral density; an enhanced glucose tolerance; developmental disorders including abnormal kidney development marked by kidney agenesis; embryonic lethality; or embryonic lethality wherein heterozygous adults exhibited decreased serum IgM, IgG1, IgG2a, IgG2b and IgG3 levels.

292. (New) An agent identified by the method of Claim 272.

293. (New) The agent of Claim 292 which is an agonist or antagonist of a PRO224, PRO9783, PRO1108, PRO34000, PRO240, PRO943, hu A33, PRO230, PRO178, PRO1199, PRO4333, PRO1336, PRO19598, PRO1083, hu TRPM2 or PRO1801 polypeptide.

294. (New) The agent of Claim 293, wherein the agonist is an anti-PRO224, anti-PRO9783, anti-PRO1108, anti-PRO34000, anti-PRO240, anti-PRO943, anti-hu A33, anti-PRO230, anti-PRO178, anti-PRO1199, anti-PRO4333, anti-PRO1336, anti-PRO19598, anti-PRO1083, anti-hu TRPM2 or anti-PRO1801 antibody.

295. (New) The agent of Claim 293, wherein the antagonist is an anti-PRO224, anti-PRO9783, anti-PRO1108, anti-PRO34000, anti-PRO240, anti-PRO943, anti-hu A33, anti-PRO230, anti-PRO178, anti-PRO1199, anti-PRO4333, anti-PRO1336, anti-PRO19598, anti-PRO1083, anti-hu TRPM2 or anti-PRO1801 antibody.

296. (New) A method of identifying an agent that modulates a physiological characteristic associated with a disruption of a gene which encodes for a PRO224, PRO9783, PRO1108, PRO34000, PRO240, PRO943, hu A33, PRO230, PRO178, PRO1199, PRO4333, PRO1336, PRO19598, PRO1083, hu TRPM2 or PRO1801 polypeptide, the method comprising:

(a) providing a non-human transgenic animal whose genome comprises a disruption of a gene which is an ortholog of a human gene that encodes for a PRO224, PRO9783, PRO1108,

PRO34000, PRO240, PRO943, hu A33, PRO230, PRO178, PRO1199, PRO4333, PRO1336, PRO19598, PRO1083, hu TRPM2 or PRO1801 polypeptide;

(b) measuring a physiological characteristic exhibited by the non-human transgenic animal of (a);

(c) comparing the measured physiological characteristic of (b) with that of a gender matched wild-type animal, wherein the physiological characteristic exhibited by the non-human transgenic animal that differs from the physiological characteristic exhibited by the wild-type animal is identified as a physiological characteristic associated with gene disruption;

(d) administering a test agent to the non-human transgenic animal of (a); and

(e) determining whether the physiological characteristic associated with gene disruption is modulated.

297. (New) The method of Claim 296, wherein the non-human transgenic animal exhibits at least one of the following physiological characteristics compared with gender matched wild-type littermates: a decreased anxiety-like response during open field activity testing; an increased anxiety-like response during open field activity testing; balding, exothalamus observations, and piloerection observations in functional observation battery (FOB) testing; an increased mean artery-to-vein ratio associated with retinal degeneration; developing cataracts; an increased mean serum cholesterol level; an increased mean serum triglyceride level; a decreased mean serum insulin level, a decreased mean percentage of B cells in the spleen and lymph node; a decreased mean serum IgG2a response to an ovalbumin challenge; decreased mean serum IgA levels; an increased mean serum IgG2a response to an ovalbumin challenge; increased mean serum IgM, IgG1, IgG2a and IgG2b levels; increased mean serum IgM, IgA and IgG3 levels; increased mean serum IgM, IgG1, IgG2a and IgG2b levels; an increased mean percentage of CD4 cells and a decreased mean percentage of CD8 cells in spleen and thymus; mobilization of neutrophils in response to peritoneal inflammation; an enhanced DDS-induced colitis response; an enhanced ConA-induced hepatitis response; a decreased skin fibroblast proliferation; a decreased volumetric bone mineral density, a decreased bone mineral content index (BMC/LBM), and a decreased mean bone mineral density in total body, femur and vertebrae; a decreased mean bone

mineral density, a decreased mean trabecular bone volume, decreased thickness, and decreased connectivity density; a decreased body weight and length, decreased total tissue mass and lean body mass, a decreased femoral midshaft cross-sectional area with decreased alkaline phosphatase levels; growth retardation with decreased body weight and length, total tissue mass, and lean body mass; a diaphragmatic hernia; an increased total tissue mass, increased lean body mass, increased bone mineral content, increased total body and increased femoral bone mineral density; an enhanced glucose tolerance; developmental disorders including abnormal kidney development marked by kidney agenesis; embryonic lethality; or embryonic lethality wherein heterozygous adults exhibited decreased serum IgM, IgG1, IgG2a, IgG2b and IgG3 levels.

298. (New) An agent identified by the method of Claim 296.

299. (New) The agent of Claim 298 which is an agonist or antagonist of a PRO224, PRO9783, PRO1108, PRO34000, PRO240, PRO943, hu A33, PRO230, PRO178, PRO1199, PRO4333, PRO1336, PRO19598, PRO1083, hu TRPM2 or PRO1801 polypeptide.

300. (New) The agent of Claim 299, wherein the agonist is an anti-PRO224, anti-PRO9783, anti-PRO1108, anti-PRO34000, anti-PRO240, anti-PRO943, anti-hu A33, anti-PRO230, anti-PRO178, anti-PRO1199, anti-PRO4333, anti-PRO1336, anti-PRO19598, anti-PRO1083, anti-hu TRPM2 or anti-PRO1801 antibody.

301. (New) The agent of Claim 299, wherein the antagonist is an anti-PRO224, anti-PRO9783, anti-PRO1108, anti-PRO34000, anti-PRO240, anti-PRO943, anti-hu A33, anti-PRO230, anti-PRO178, anti-PRO1199, anti-PRO4333, anti-PRO1336, anti-PRO19598, anti-PRO1083, anti-hu TRPM2 or anti-PRO1801 antibody.

302. (New) A method of identifying an agent which modulates a behavior associated with a disruption of a gene which encodes for a PRO224, PRO9783, PRO1108, PRO34000, PRO240, PRO943, hu A33, PRO230, PRO178, PRO1199, PRO4333, PRO1336, PRO19598, PRO1083, hu TRPM2 or PRO1801 polypeptide, the method comprising:

(a) providing a non-human transgenic animal whose genome comprises a disruption of a gene which is an ortholog of a human gene that encodes for a PRO224, PRO9783, PRO1108, PRO34000, PRO240, PRO943, hu A33, PRO230, PRO178, PRO1199, PRO4333, PRO1336, PRO19598, PRO1083, hu TRPM2 or PRO1801 polypeptide;

(b) observing the behavior exhibited by the non-human transgenic animal of (a);

(c) comparing the observed behavior of (b) with that of a gender matched wild-type animal, wherein the observed behavior exhibited by the non-human transgenic animal that differs from the observed behavior exhibited by the wild-type animal is identified as a behavior associated with gene disruption;

(d) administering a test agent to the non-human transgenic animal of (a); and

(e) determining whether the agent modulates the behavior associated with gene disruption.

303. (New) The method of Claim 302, wherein the behavior is an increased anxiety-like response during open field activity testing.

304. (New) The method of Claim 302, wherein the behavior is a decreased anxiety-like response during open field activity testing.

305. (New) The method of Claim 302, wherein the behavior is an abnormal circadian rhythm during home-cage activity testing.

306. (New) The method of Claim 302, wherein the behavior is an enhanced motor coordination during inverted screen testing.

307. (New) The method of Claim 302, wherein the behavior is an impaired motor coordination during inverted screen testing.
308. (New) The method of Claim 302, wherein the behavior is depression, generalized anxiety disorders, attention deficit disorder, sleep disorder, hyperactivity disorder, obsessive compulsive disorder, schizophrenia, cognitive disorders, hyperalgesia or sensory disorders.
309. (New) An agent identified by the method of Claim 302.
310. (New) The agent of Claim 309 which is an agonist or antagonist of a PRO224, PRO9783, PRO1108, PRO34000, PRO240, PRO943, hu A33, PRO230, PRO178, PRO1199, PRO4333, PRO1336, PRO19598, PRO1083, hu TRPM2 or PRO1801 polypeptide.
311. (New) The agent of Claim 310, wherein the agonist is an anti-PRO224, anti-PRO9783, anti-PRO1108, anti-PRO34000, anti-PRO240, anti-PRO943, anti-hu A33, anti-PRO230, anti-PRO178, anti-PRO1199, anti-PRO4333, anti-PRO1336, anti-PRO19598, anti-PRO1083, anti-hu TRPM2 or anti-PRO1801 antibody.
312. (New) The agent of Claim 310, wherein the antagonist is an anti-PRO224, anti-PRO9783, anti-PRO1108, anti-PRO34000, anti-PRO240, anti-PRO943, anti-hu A33, anti-PRO230, anti-PRO178, anti-PRO1199, anti-PRO4333, anti-PRO1336, anti-PRO19598, anti-PRO1083, anti-hu TRPM2 or anti-PRO1801 antibody.
313. (New) A method of identifying an agent that ameliorates or modulates a neurological disorder; a cardiovascular, endothelial or angiogenic disorder; an eye abnormality; an immunological disorder; an oncological disorder; a bone metabolic abnormality or disorder; a lipid metabolic disorder; or a developmental abnormality associated with a disruption in a gene which encodes for a PRO224, PRO9783, PRO1108, PRO34000, PRO240, PRO943, hu A33, PRO230, PRO178, PRO1199, PRO4333, PRO1336, PRO19598, PRO1083, hu TRPM2 or

PRO1801 polypeptide, the method comprising:

- (a) providing a non-human transgenic animal whose genome comprises a disruption of a gene which is an ortholog of a human gene that encodes for a PRO224, PRO9783, PRO1108, PRO34000, PRO240, PRO943, hu A33, PRO230, PRO178, PRO1199, PRO4333, PRO1336, PRO19598, PRO1083, hu TRPM2 or PRO1801 polypeptide;
- (b) administering a test agent to said non-human transgenic animal; and
- (c) determining whether said test agent ameliorates or modulates the neurological disorder; cardiovascular, endothelial or angiogenic disorder; eye abnormality; immunological disorder; oncological disorder; bone metabolic abnormality or disorder; lipid metabolic disorder; or developmental abnormality in the non-human transgenic animal.

314. (New) The method of Claim 313, wherein the neurological disorder is an increased anxiety-like response during open field activity testing.

315. (New) The method of Claim 313, wherein the neurological disorder is a decreased anxiety-like response during open field activity testing.

316. (New) The method of Claim 313, wherein the neurological disorder is an abnormal circadian rhythm during home-cage activity testing.

317. (New) The method of Claim 313, wherein the neurological disorder is an enhanced motor coordination during inverted screen testing.

318. (New) The method of Claim 313, wherein the neurological disorder is an impaired motor coordination during inverted screen testing.

319. (New) The method of Claim 313, wherein the neurological disorder is depression, generalized anxiety disorders, attention deficit disorder, sleep disorder, hyperactivity disorder, obsessive compulsive disorder, schizophrenia, cognitive disorders, hyperalgesia or sensory

disorders.

320. (New) The method of Claim 313, wherein the eye abnormality is a retinal abnormality.

321. (New) The method of Claim 313, wherein the eye abnormality is consistent with vision problems or blindness.

322. (New) The method of Claim 320, wherein the retinal abnormality is consistent with retinitis pigmentosa.

323. (New) The method of Claim 320, wherein the retinal abnormality is characterized by retinal degeneration or retinal dysplasia.

324. (New) The method of Claim 320, wherein the retinal abnormality is consistent with retinal dysplasia, various retinopathies, including retinopathy of prematurity, retrolental fibroplasia, neovascular glaucoma, age-related macular degeneration, diabetic macular edema, corneal neovascularization, corneal graft neovascularization, corneal graft rejection, retinal/choroidal neovascularization, neovascularization of the angle (rubeosis), ocular neovascular disease, vascular restenosis, arteriovenous malformations (AVM), meningioma, hemangioma, angiofibroma, thyroid hyperplasias (including Grave's disease), corneal and other tissue transplantation, retinal artery obstruction or occlusion; retinal degeneration causing secondary atrophy of the retinal vasculature, retinitis pigmentosa, macular dystrophies, Stargardt's disease, congenital stationary night blindness, choroideremia, gyrate atrophy, Leber's congenital amaurosis, retinoschisis disorders, Wagner's syndrome, Usher syndromes, Zellweger syndrome, Saldino-Mainzer syndrome, Senior-Loken syndrome, Bardet-Biedl syndrome, Alport's syndrome, Alstrom's syndrome, Cockayne's syndrome, dysplasia spondyloepiphysearia congenita, Flynn-Aird syndrome, Friedreich ataxia, Hallgren syndrome, Marshall syndrome, Albers-Schnoberg disease, Refsum's disease, Kearns-Sayre syndrome, Waardenburg's syndrome, Alagile syndrome, myotonic dystrophy, olivopontocerebellar atrophy, Pierre-Marie syndrome,

Stickler syndrome, carotinemeia, cystinosis, Wolfram syndrome, Bassen-Kornzweig syndrome, abetalipoproteinemia, incontinentia pigmenti, Batten's disease, mucopolysaccharidoses, homocystinuria, or mannosidosis.

325. (New) The method of Claim 313, wherein the eye abnormality is a cataract.

326. (New) The method of Claim 325, wherein the cataract is a systemic disease such as human Down's syndrome, Hallerman-Streiff syndrome, Lowe syndrome, galactosemia, Marfan syndrome, Trismoy 13-15, Alport syndrome, myotonic dystrophy, Fabry disease, hypoparathyroidism or Conradi syndrome.

327. (New) The method of Claim 313, wherein the developmental abnormality comprises embryonic lethality or reduced viability.

328. (New) The method of Claim 313, wherein the cardiovascular, endothelial or angiogenic disorders are arterial diseases, such as diabetes mellitus; papilledema; optic atrophy; atherosclerosis; angina; myocardial infarctions such as acute myocardial infarctions, cardiac hypertrophy, and heart failure such as congestive heart failure; hypertension; inflammatory vasculitides; Reynaud's disease and Reynaud's phenomenon; aneurysms and arterial restenosis; venous and lymphatic disorders such as thrombophlebitis, lymphangitis, and lymphedema; peripheral vascular disease; cancer such as vascular tumors, *e.g.*, hemangioma (capillary and cavernous), glomus tumors, telangiectasia, bacillary angiomatosis, hemangioendothelioma, angiosarcoma, haemangiopericytoma, Kaposi's sarcoma, lymphangioma, and lymphangiosarcoma; tumor angiogenesis; trauma such as wounds, burns, and other injured tissue, implant fixation, scarring; ischemia reperfusion injury; rheumatoid arthritis; cerebrovascular disease; renal diseases such as acute renal failure, or osteoporosis.

329. (New) The method of Claim 313, wherein the immunological disorders are systemic lupus erythematosus; rheumatoid arthritis; juvenile chronic arthritis; spondyloarthropathies; systemic sclerosis (scleroderma); idiopathic inflammatory myopathies (dermatomyositis, polymyositis); Sjögren's syndrome; systemic vasculitis; sarcoidosis; autoimmune hemolytic anemia (immune pancytopenia, paroxysmal nocturnal hemoglobinuria); autoimmune thrombocytopenia (idiopathic thrombocytopenic purpura, immune-mediated thrombocytopenia); thyroiditis (Grave's disease, Hashimoto's thyroiditis, juvenile lymphocytic thyroiditis, atrophic thyroiditis); diabetes mellitus; immune-mediated renal disease (glomerulonephritis, tubulointerstitial nephritis); demyelinating diseases of the central and peripheral nervous systems such as multiple sclerosis, idiopathic demyelinating polyneuropathy or Guillain-Barré syndrome, and chronic inflammatory demyelinating polyneuropathy; hepatobiliary diseases such as infectious hepatitis (hepatitis A, B, C, D, E and other non-hepatotropic viruses), autoimmune chronic active hepatitis, primary biliary cirrhosis, granulomatous hepatitis, and sclerosing cholangitis; inflammatory bowel disease (ulcerative colitis: Crohn's disease); gluten-sensitive enteropathy, and Whipple's disease; autoimmune or immune-mediated skin diseases including bullous skin diseases, erythema multiforme and contact dermatitis, psoriasis; allergic diseases such as asthma, allergic rhinitis, atopic dermatitis, food hypersensitivity and urticaria; immunologic diseases of the lung such as eosinophilic pneumonia, idiopathic pulmonary fibrosis and hypersensitivity pneumonitis; or transplantation associated diseases including graft rejection and graft -versus-host disease.

330. (New) The method of Claim 313, wherein said bone metabolic abnormality or disorder is arthritis, osteoporosis or osteopetrosis.

331. (New) The method of Claim 313, wherein the non-human transgenic animal exhibits at least one of the following physiological characteristics compared with gender matched wild-type littermates: a decreased anxiety-like response during open field activity testing; an increased anxiety-like response during open field activity testing; balding, exothalamus observations, and piloerection observations in functional observation battery (FOB) testing; an increased mean

artery-to-vein ratio associated with retinal degeneration; developing cataracts; an increased mean serum cholesterol level; an increased mean serum triglyceride level; a decreased mean serum insulin level, a decreased mean percentage of B cells in the spleen and lymph node; a decreased mean serum IgG2a response to an ovalbumin challenge; decreased mean serum IgA levels; an increased mean serum IgG2a response to an ovalbumin challenge; increased mean serum IgM, IgG1, IgG2a and IgG2b levels; increased mean serum IgM, IgA and IgG3 levels; increased mean serum IgM, IgG1, IgG2a and IgG2b levels; an increased mean percentage of CD4 cells and a decreased mean percentage of CD8 cells in spleen and thymus; mobilization of neutrophils in response to peritoneal inflammation; an enhanced DDS-induced colitis response; an enhanced ConA-induced hepatitis response; a decreased skin fibroblast proliferation; a decreased volumetric bone mineral density, a decreased bone mineral content index (BMC/LBM), and a decreased mean bone mineral density in total body, femur and vertebrae; a decreased mean bone mineral density, a decreased mean trabecular bone volume, decreased thickness, and decreased connectivity density; a decreased body weight and length, decreased total tissue mass and lean body mass, a decreased femoral midshaft cross-sectional area with decreased alkaline phosphatase levels; growth retardation with decreased body weight and length, total tissue mass, and lean body mass; a diaphragmatic hernia; an increased total tissue mass, increased lean body mass, increased bone mineral content, increased total body and increased femoral bone mineral density; an enhanced glucose tolerance; developmental disorders including abnormal kidney development marked by kidney agenesis; embryonic lethality; or embryonic lethality wherein heterozygous adults exhibited decreased serum IgM, IgG1, IgG2a, IgG2b and IgG3 levels.

332. (New) An agent identified by the method of Claim 313.

333. (New) The agent of Claim 332 which is an agonist or antagonist of a PRO224, PRO9783, PRO1108, PRO34000, PRO240, PRO943, hu A33, PRO230, PRO178, PRO1199, PRO4333, PRO1336, PRO19598, PRO1083, hu TRPM2 or PRO1801 polypeptide.

334. (New) The agent of Claim 333, wherein the agonist is an anti-PRO224, anti-PRO9783, anti-PRO1108, anti-PRO34000, anti-PRO240, anti-PRO943, anti-hu A33, anti-PRO230, anti-PRO178, anti-PRO1199, anti-PRO4333, anti-PRO1336, anti-PRO19598, anti-PRO1083, anti-hu TRPM2 or anti-PRO1801 antibody.

335. (New) The agent of Claim 333, wherein the antagonist is an anti-PRO224, anti-PRO9783, anti-PRO1108, anti-PRO34000, anti-PRO240, anti-PRO943, anti-hu A33, anti-PRO230, anti-PRO178, anti-PRO1199, anti-PRO4333, anti-PRO1336, anti-PRO19598, anti-PRO1083, anti-hu TRPM2 or anti-PRO1801 antibody.

336. (New) A therapeutic agent identified by the method of Claim 313.

337. (New) A method of identifying an agent that modulates the expression of a PRO224, PRO9783, PRO1108, PRO34000, PRO240, PRO943, hu A33, PRO230, PRO178, PRO1199, PRO4333, PRO1336, PRO19598, PRO1083, hu TRPM2 or PRO1801 polypeptide, the method comprising:

(a) contacting a test agent with a host cell expressing a PRO224, PRO9783, PRO1108, PRO34000, PRO240, PRO943, hu A33, PRO230, PRO178, PRO1199, PRO4333, PRO1336, PRO19598, PRO1083, hu TRPM2 or PRO1801 polypeptide; and

(b) determining whether the test agent modulates the expression of the PRO224, PRO9783, PRO1108, PRO34000, PRO240, PRO943, hu A33, PRO230, PRO178, PRO1199, PRO4333, PRO1336, PRO19598, PRO1083, hu TRPM2 or PRO1801 polypeptide by the host cell.

338. (New) An agent identified by the method of Claim 337.

339. (New) The agent of Claim 338 which is an agonist or antagonist of a PRO224, PRO9783, PRO1108, PRO34000, PRO240, PRO943, hu A33, PRO230, PRO178, PRO1199, PRO4333, PRO1336, PRO19598, PRO1083, hu TRPM2 or PRO1801 polypeptide.

340. (New) The agent of Claim 339, wherein the agonist is an anti-PRO224, anti-PRO9783, anti-PRO1108, anti-PRO34000, anti-PRO240, anti-PRO943, anti-hu A33, anti-PRO230, anti-PRO178, anti-PRO1199, anti-PRO4333, anti-PRO1336, anti-PRO19598, anti-PRO1083, anti-hu TRPM2 or anti-PRO1801 antibody.

341. (New) The agent of Claim 339, wherein the antagonist is an anti-PRO224, anti-PRO9783, anti-PRO1108, anti-PRO34000, anti-PRO240, anti-PRO943, anti-hu A33, anti-PRO230, anti-PRO178, anti-PRO1199, anti-PRO4333, anti-PRO1336, anti-PRO19598, anti-PRO1083, anti-hu TRPM2 or anti-PRO1801 antibody.

342. (New) A method of evaluating a therapeutic agent capable of affecting a condition associated with a disruption of a gene which encodes for a PRO224, PRO9783, PRO1108, PRO34000, PRO240, PRO943, hu A33, PRO230, PRO178, PRO1199, PRO4333, PRO1336, PRO19598, PRO1083, hu TRPM2 or PRO1801 polypeptide, the method comprising:

- (a) providing a non-human transgenic animal whose genome comprises a disruption of a gene which is an ortholog of a human gene that encodes for the PRO224, PRO9783, PRO1108, PRO34000, PRO240, PRO943, hu A33, PRO230, PRO178, PRO1199, PRO4333, PRO1336, PRO19598, PRO1083, hu TRPM2 or PRO1801 polypeptide;
- (b) measuring a physiological characteristic of the non-human transgenic animal of (a);
- (c) comparing the measured physiological characteristic of (b) with that of a gender matched wild-type animal, wherein the physiological characteristic of the non-human transgenic animal that differs from the physiological characteristic of the wild-type animal is identified as a condition resulting from the gene disruption in the non-human transgenic animal;
- (d) administering a test agent to the non-human transgenic animal of (a); and
- (e) evaluating the effects of the test agent on the identified condition associated with gene disruption in the non-human transgenic animal.

343. (New) The method of Claim 342, wherein the condition is a neurological disorder; a cardiovascular, endothelial or angiogenic disorder; an eye abnormality; an immunological disorder; an oncological disorder; a bone metabolic abnormality or disorder; a lipid metabolic disorder; or a developmental abnormality.

344. (New) A therapeutic agent identified by the method of Claim 342.

345. (New) The therapeutic agent of Claim 344 which is an agonist or antagonist of a PRO224, PRO9783, PRO1108, PRO34000, PRO240, PRO943, hu A33, PRO230, PRO178, PRO1199, PRO4333, PRO1336, PRO19598, PRO1083, hu TRPM2 or PRO1801 polypeptide.

346. (New) The therapeutic agent of Claim 345, wherein the agonist is an anti-PRO224, anti-PRO9783, anti-PRO1108, anti-PRO34000, anti-PRO240, anti-PRO943, anti-hu A33, anti-PRO230, anti-PRO178, anti-PRO1199, anti-PRO4333, anti-PRO1336, anti-PRO19598, anti-PRO1083, anti-hu TRPM2 or anti-PRO1801 antibody.

347. (New) The therapeutic agent of Claim 345, wherein the antagonist is an anti-PRO224, anti-PRO9783, anti-PRO1108, anti-PRO34000, anti-PRO240, anti-PRO943, anti-hu A33, anti-PRO230, anti-PRO178, anti-PRO1199, anti-PRO4333, anti-PRO1336, anti-PRO19598, anti-PRO1083, anti-hu TRPM2 or anti-PRO1801 antibody.

348. (New) A pharmaceutical composition comprising the therapeutic agent of Claim 344.

349. (New) A method of treating or preventing or ameliorating a neurological disorder; cardiovascular, endothelial or angiogenic disorder; immunological disorder; oncological disorder; bone metabolic abnormality or disorder, or embryonic lethality associated with the disruption of a gene which encodes for a PRO224, PRO9783, PRO1108, PRO34000, PRO240, PRO943, hu A33, PRO230, PRO178, PRO1199, PRO4333, PRO1336, PRO19598, PRO1083, hu TRPM2 or PRO1801 polypeptide, the method comprising administering to a subject in need

of such treatment whom may already have the disorder, or may be prone to have the disorder or may be in whom the disorder is to be prevented, a therapeutically effective amount of the therapeutic agent of Claim 336, or agonists or antagonists thereof, thereby effectively treating or preventing or ameliorating said disorder.

350. (New) The method of Claim 349, wherein the neurological disorder is an increased anxiety-like response during open field activity testing.

351. (New) The method of Claim 349, wherein the neurological disorder is a decreased anxiety-like response during open field activity testing.

352. (New) The method of Claim 349, wherein the neurological disorder is an abnormal circadian rhythm during home-cage activity testing.

353. (New) The method of Claim 349, wherein the neurological disorder is an enhanced motor coordination during inverted screen testing.

354. (New) The method of Claim 349, wherein the neurological disorder is an impaired motor coordination during inverted screen testing.

355. (New) The method of Claim 349, wherein the neurological disorder is depression, generalized anxiety disorders, attention deficit disorder, sleep disorder, hyperactivity disorder, obsessive compulsive disorder, schizophrenia, cognitive disorders, hyperalgesia or sensory disorders.

356. (New) The method of Claim 349, wherein the eye abnormality is a retinal abnormality.

357. (New) The method of Claim 349, wherein the eye abnormality is consistent with vision problems or blindness.

358. (New) The method of Claim 356, wherein the retinal abnormality is consistent with retinitis pigmentosa.

359. (New) The method of Claim 356, wherein the retinal abnormality is characterized by retinal degeneration or retinal dysplasia.

360. (New) The method of Claim 356, wherein the retinal abnormality is consistent with retinal dysplasia, various retinopathies, including retinopathy of prematurity, retrolental fibroplasia, neovascular glaucoma, age-related macular degeneration, diabetic macular edema, corneal neovascularization, corneal graft neovascularization, corneal graft rejection, retinal/choroidal neovascularization, neovascularization of the angle (rubeosis), ocular neovascular disease, vascular restenosis, arteriovenous malformations (AVM), meningioma, hemangioma, angiofibroma, thyroid hyperplasias (including Grave's disease), corneal and other tissue transplantation, retinal artery obstruction or occlusion; retinal degeneration causing secondary atrophy of the retinal vasculature, retinitis pigmentosa, macular dystrophies, Stargardt's disease, congenital stationary night blindness, choroideremia, gyrate atrophy, Leber's congenital amaurosis, retinoschisis disorders, Wagner's syndrome, Usher syndromes, Zellweger syndrome, Saldino-Mainzer syndrome, Senior-Loken syndrome, Bardet-Biedl syndrome, Alport's syndrome, Alstrom's syndrome, Cockayne's syndrome, dysplasia spondyloepiphysearia congenita, Flynn-Aird syndrome, Friedreich ataxia, Hallgren syndrome, Marshall syndrome, Albers-Schnoberg disease, Refsum's disease, Kearns-Sayre syndrome, Waardenburg's syndrome, Alagille syndrome, myotonic dystrophy, olivopontocerebellar atrophy, Pierre-Marie syndrome, Stickler syndrome, carotinemia, cystinosis, Wolfram syndrome, Bassen-Kornzweig syndrome, abetalipoproteinemia, incontinentia pigmenti, Batten's disease, mucopolysaccharidoses, homocystinuria, or mannosidosis.

361. (New) The method of Claim 349, wherein the eye abnormality is a cataract.

362. (New) The method of Claim 361, wherein the cataract is a systemic disease such as human Down's syndrome, Hallerman-Streiff syndrome, Lowe syndrome, galactosemia, Marfan syndrome, Trismoy 13-15, Alport syndrome, myotonic dystrophy, Fabry disease, hypoparathyroidism or Conradi syndrome.

363. (New) The method of Claim 349, wherein the developmental abnormality comprises embryonic lethality or reduced viability.

364. (New) The method of Claim 349, wherein the cardiovascular, endothelial or angiogenic disorders are arterial diseases, such as diabetes mellitus; papilledema; optic atrophy; atherosclerosis; angina; myocardial infarctions such as acute myocardial infarctions, cardiac hypertrophy, and heart failure such as congestive heart failure; hypertension; inflammatory vasculitides; Reynaud's disease and Reynaud's phenomenon; aneurysms and arterial restenosis; venous and lymphatic disorders such as thrombophlebitis, lymphangitis, and lymphedema; peripheral vascular disease; cancer such as vascular tumors, *e.g.*, hemangioma (capillary and cavernous), glomus tumors, telangiectasia, bacillary angiomatosis, hemangioendothelioma, angiosarcoma, haemangiopericytoma, Kaposi's sarcoma, lymphangioma, and lymphangiosarcoma; tumor angiogenesis; trauma such as wounds, burns, and other injured tissue, implant fixation, scarring; ischemia reperfusion injury; rheumatoid arthritis; cerebrovascular disease; renal diseases such as acute renal failure, or osteoporosis.

365. (New) The method of Claim 349, wherein the immunological disorders are systemic lupus erythematosus; rheumatoid arthritis; juvenile chronic arthritis; spondyloarthropathies; systemic sclerosis (scleroderma); idiopathic inflammatory myopathies (dermatomyositis, polymyositis); Sjögren's syndrome; systemic vasculitis; sarcoidosis; autoimmune hemolytic anemia (immune pancytopenia, paroxysmal nocturnal hemoglobinuria); autoimmune thrombocytopenia (idiopathic thrombocytopenic purpura, immune-mediated thrombocytopenia); thyroiditis (Grave's disease, Hashimoto's thyroiditis, juvenile lymphocytic thyroiditis, atrophic

thyroiditis); diabetes mellitus; immune-mediated renal disease (glomerulonephritis, tubulointerstitial nephritis); demyelinating diseases of the central and peripheral nervous systems such as multiple sclerosis, idiopathic demyelinating polyneuropathy or Guillain-Barré syndrome, and chronic inflammatory demyelinating polyneuropathy; hepatobiliary diseases such as infectious hepatitis (hepatitis A, B, C, D, E and other non-hepatotropic viruses), autoimmune chronic active hepatitis, primary biliary cirrhosis, granulomatous hepatitis, and sclerosing cholangitis; inflammatory bowel disease (ulcerative colitis: Crohn's disease); gluten-sensitive enteropathy, and Whipple's disease; autoimmune or immune-mediated skin diseases including bullous skin diseases, erythema multiforme and contact dermatitis, psoriasis; allergic diseases such as asthma, allergic rhinitis, atopic dermatitis, food hypersensitivity and urticaria; immunologic diseases of the lung such as eosinophilic pneumonia, idiopathic pulmonary fibrosis and hypersensitivity pneumonitis; or transplantation associated diseases including graft rejection and graft-versus-host disease.

366. (New) The method of Claim 349, wherein said bone metabolic abnormality or disorder is arthritis, osteoporosis or osteopetrosis.

367. (New) A method of modulating a phenotype associated with a disruption of a gene which encodes for a PRO224, PRO9783, PRO1108, PRO34000, PRO240, PRO943, hu A33, PRO230, PRO178, PRO1199, PRO4333, PRO1336, PRO19598, PRO1083, hu TRPM2 or PRO1801 polypeptide, the method comprising administering to a subject whom may already have the phenotype, or may be prone to have the phenotype or may be in whom the phenotype is to be prevented, an effective amount of the agent of Claim 292, or agonists or antagonists thereof, thereby effectively modulating the phenotype.

368. (New) A method of modulating a physiological characteristic associated with a disruption of a gene which encodes for a PRO224, PRO9783, PRO1108, PRO34000, PRO240, PRO943, hu A33, PRO230, PRO178, PRO1199, PRO4333, PRO1336, PRO19598, PRO1083, hu TRPM2 or PRO1801 polypeptide, the method comprising administering to a subject whom

may already exhibit the physiological characteristic, or may be prone to exhibit the physiological characteristic or may be in whom the physiological characteristic is to be prevented, an effective amount of the agent of Claim 298, or agonists or antagonists thereof, thereby effectively modulating the physiological characteristic.

369. (New) A method of modulating a behavior associated with a disruption of a gene which encodes for a PRO224, PRO9783, PRO1108, PRO34000, PRO240, PRO943, hu A33, PRO230, PRO178, PRO1199, PRO4333, PRO1336, PRO19598, PRO1083, hu TRPM2 or PRO1801 polypeptide, the method comprising administering to a subject whom may already exhibit the behavior, or may be prone to exhibit the behavior or may be in whom the exhibited behavior is to be prevented, an effective amount of the agent of Claim 309, or agonists or antagonists thereof, thereby effectively modulating the behavior.

370. (New) A method of modulating the expression of a PRO224, PRO9783, PRO1108, PRO34000, PRO240, PRO943, hu A33, PRO230, PRO178, PRO1199, PRO4333, PRO1336, PRO19598, PRO1083, hu TRPM2 or PRO1801 polypeptide, the method comprising administering to a host cell expressing said PRO224, PRO9783, PRO1108, PRO34000, PRO240, PRO943, hu A33, PRO230, PRO178, PRO1199, PRO4333, PRO1336, PRO19598, PRO1083, hu TRPM2 or PRO1801 polypeptide, an effective amount of the agent of Claim 338, or agonists or antagonists thereof, thereby effectively modulating the expression of said polypeptide.

371. (New) A method of modulating a condition associated with a disruption of a gene which encodes for a PRO224, PRO9783, PRO1108, PRO34000, PRO240, PRO943, hu A33, PRO230, PRO178, PRO1199, PRO4333, PRO1336, PRO19598, PRO1083, hu TRPM2 or PRO1801 polypeptide, the method comprising administering to a subject whom may have the condition, or may be prone to have the condition or may be in whom the condition is to be prevented, a therapeutically effective amount of the therapeutic agent of Claim 344, or agonists or antagonists thereof, thereby effectively modulating the condition.

372. (New) A method of identifying an agent that mimics a condition or phenotype associated with a disruption in a gene which encodes a PRO224, PRO9783, PRO1108, PRO34000, PRO240, PRO943, hu A33, PRO230, PRO178, PRO1199, PRO4333, PRO1336, PRO19598, PRO1083, hu TRPM2 or PRO1801 polypeptide, the method comprising:

- (a) providing a non-human transgenic animal whose genome comprises a disruption of a gene which is an ortholog of a human gene that encodes a PRO224, PRO9783, PRO1108, PRO34000, PRO240, PRO943, hu A33, PRO230, PRO178, PRO1199, PRO4333, PRO1336, PRO19598, PRO1083, hu TRPM2 or PRO1801 polypeptide;
- (b) measuring a physiological characteristic of the non-human transgenic animal of (a);
- (c) comparing the measured physiological characteristic of (b) with that of a gender matched wild-type animal, wherein the physiological characteristic of the non-human transgenic animal that differs from the physiological characteristic of the gender matched wild-type animal is identified as a condition or phenotype resulting from the gene disruption in the non-human transgenic animal;
- (d) administering a test agent to said gender matched wild-type animal; and
- (e) determining whether said test agent mimics the condition or phenotype initially observed in the non-human transgenic animal.

373. (New) The method of Claim 372, wherein the condition or phenotype associated with the disruption of the gene which is an ortholog of a human gene that encodes a PRO224, PRO9783, PRO1108, PRO34000, PRO240, PRO943, hu A33, PRO230, PRO178, PRO1199, PRO4333, PRO1336, PRO19598, PRO1083, hu TRPM2 or PRO1801 polypeptide is enhanced glucose tolerance.

374. (New) The method of Claim 372, wherein the condition or phenotype associated with the disruption of the gene which is an ortholog of a human gene that encodes a PRO224, PRO9783, PRO1108, PRO34000, PRO240, PRO943, hu A33, PRO230, PRO178, PRO1199, PRO4333,

PRO1336, PRO19598, PRO1083, hu TRPM2 or PRO1801 polypeptide is increased insulin sensitivity.

375. (New) An agent identified by the method of Claim 372.

376. (New) The agent of Claim 375 which is an antagonist of a PRO224, PRO9783, PRO1108, PRO34000, PRO240, PRO943, hu A33, PRO230, PRO178, PRO1199, PRO4333, PRO1336, PRO19598, PRO1083, hu TRPM2 or PRO1801 polypeptide.

377. (New) The agent of Claim 376, wherein the antagonist is an anti-PRO224, anti-PRO9783, anti-PRO1108, anti-PRO34000, anti-PRO240, anti-PRO943, anti-hu A33, anti-PRO230, anti-PRO178, anti-PRO1199, anti-PRO4333, anti-PRO1336, anti-PRO19598, anti-PRO1083, anti-hu TRPM2 or anti-PRO1801 antibody.

378. (New) A method of mimicking a condition or phenotype associated with a disruption of a gene which encodes a PRO224, PRO9783, PRO1108, PRO34000, PRO240, PRO943, hu A33, PRO230, PRO178, PRO1199, PRO4333, PRO1336, PRO19598, PRO1083, hu TRPM2 or PRO1801 polypeptide, the method comprising administering to a subject in whom the condition or phenotype is to be mimicked, an effective amount of the agent of Claim 375 or an antagonist of a PRO224, PRO9783, PRO1108, PRO34000, PRO240, PRO943, hu A33, PRO230, PRO178, PRO1199, PRO4333, PRO1336, PRO19598, PRO1083, hu TRPM2 or PRO1801 polypeptide, thereby effectively mimicking the condition or phenotype.

379. (New) The method of Claim 378, wherein the condition or phenotype associated with the disruption of the gene which is an ortholog of a human gene that encodes a PRO224, PRO9783, PRO1108, PRO34000, PRO240, PRO943, hu A33, PRO230, PRO178, PRO1199, PRO4333, PRO1336, PRO19598, PRO1083, hu TRPM2 or PRO1801 polypeptide is enhanced glucose tolerance.

380. (New) The method of Claim 378, wherein the condition or phenotype associated with the disruption of the gene which is an ortholog of a human gene that encodes a PRO224, PRO9783, PRO1108, PRO34000, PRO240, PRO943, hu A33, PRO230, PRO178, PRO1199, PRO4333, PRO1336, PRO19598, PRO1083, hu TRPM2 or PRO1801 polypeptide is increased insulin sensitivity.

381. (New) A method of evaluating a therapeutic agent capable of mimicking a condition or phenotype associated with a disruption of a gene which encodes a PRO224, PRO9783, PRO1108, PRO34000, PRO240, PRO943, hu A33, PRO230, PRO178, PRO1199, PRO4333, PRO1336, PRO19598, PRO1083, hu TRPM2 or PRO1801 polypeptide, the method comprising:

(a) providing a non-human transgenic animal whose genome comprises a disruption of a gene which is an ortholog of a human gene that encodes a PRO224, PRO9783, PRO1108, PRO34000, PRO240, PRO943, hu A33, PRO230, PRO178, PRO1199, PRO4333, PRO1336, PRO19598, PRO1083, hu TRPM2 or PRO1801 polypeptide;

(b) measuring a physiological characteristic of the non-human transgenic animal of (a);

(c) comparing the measured physiological characteristic of (b) with that of a gender matched wild-type animal, wherein the physiological characteristic of the non-human transgenic animal that differs from the physiological characteristic of the gender matched wild-type animal is identified as a condition or phenotype resulting from the gene disruption in the non-human transgenic animal;

(d) administering a test agent to said gender matched wild-type animal of (c); and

(e) evaluating the ability of the test agent to mimic the condition or phenotype associated with gene disruption in the non-human transgenic animal.

382. (New) A therapeutic agent identified by the method of Claim 381.

383. (New) The therapeutic agent of Claim 382 which is an antagonist of a PRO224, PRO9783, PRO1108, PRO34000, PRO240, PRO943, hu A33, PRO230, PRO178, PRO1199, PRO4333, PRO1336, PRO19598, PRO1083, hu TRPM2 or PRO1801 polypeptide.

384. (New) The therapeutic agent of Claim 383, wherein the antagonist is an anti-PRO224, anti-PRO9783, anti-PRO1108, anti-PRO34000, anti-PRO240, anti-PRO943, anti-hu A33, anti-PRO230, anti-PRO178, anti-PRO1199, anti-PRO4333, anti-PRO1336, anti-PRO19598, anti-PRO1083, anti-hu TRPM2 or anti-PRO1801 antibody.

385. (New) A pharmaceutical composition comprising the therapeutic agent of Claim 382.

386. (New) A method of mimicking a condition or phenotype associated with a disruption of a gene which encodes a PRO224, PRO9783, PRO1108, PRO34000, PRO240, PRO943, hu A33, PRO230, PRO178, PRO1199, PRO4333, PRO1336, PRO19598, PRO1083, hu TRPM2 or PRO1801 polypeptide, the method comprising administering to a subject in whom the condition or phenotype disorder is to be mimicked, a therapeutically effective amount of the therapeutic agent of Claim 382, or an antagonist of a PRO224, PRO9783, PRO1108, PRO34000, PRO240, PRO943, hu A33, PRO230, PRO178, PRO1199, PRO4333, PRO1336, PRO19598, PRO1083, hu TRPM2 or PRO1801 polypeptide, thereby effectively mimicking the condition or phenotype.